

Numerical study of 3D vesicles under flow: discovery of new peculiar behaviors

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The study of vesicles under flow, a model system for red blood cells (RBCs), is an essential step in understanding various intricate dynamics exhibited by RBCs *in vivo* and *in vitro*. Quantitative 3D analyses of vesicles under flow are presented. The regions of parameters to produce tumbling (TB), tank-treading (TT), vacillating-breathing (VB) and even Kayaking (K) modes are determined. New qualitative features are found: (i) a significant widening of the VB mode region in parameter space upon increasing shear rate $\dot{\gamma}$ and (ii) a striking robustness of period of TB and VB with $\dot{\gamma}$. Analytical support is also provided. These findings shed new light on the dynamics of blood flow.

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Introduction After nearly a century of research on blood, understanding of the basic blood flow mechanisms at the cellular level (at the scale of red blood cells, platelets, etc.) is still an open issue. Blood is a complex fluid and the description of its flow properties escapes the traditional Navier-Stokes law known for simple fluids (e.g. water).

To date blood flow has been described by means of phenomenological continuum models that require many assumptions which are difficult both to justify and to validate [1]. Furthermore, the modern view of complex fluids has highlighted the intimate coupling between the dynamics of the microscopic suspended entities (RBCs in the example of blood) and the flow at the global scale [2]. This implies that the macroscopic law of blood flow should carry information on the microscopic scale, such as the orientation of the cells, their individual and collective dynamics, their local concentration (hematocrit), and so on. Apart from a dilute suspension where a rheological law can be extracted analytically [3], a complete understanding of blood flow should ultimately emerge from a numerical study.

Computational approaches are, however, challenging due to the free boundary character of the RBCs (the shape is not known *a priori*) which is fixed via a subtle interplay between the local flow and the different internal modes of the RBCs (membrane bending, shear elasticity).

Under simple shear flow, RBCs exhibit *tank-treading* (TT), *tumbling* (TB), *vacillating-breathing* (VB) (aka swinging or trembling) and *kayaking* (K) (see movies of the four modes [4]). These dynamics should have an impact on the macroscopic flow. These modes are shared both by vesicles [3, 5, 6, 7, 8, 11, 12, 13, 14, 15, 16, 17] (made of a pure bilayer phospholipid membrane) and RBCs [18], which, apart from having the same type of phospholipid membrane, are endowed with a cytoskeleton (a cross-linked network of proteins lying underneath the RBC membrane). A systematic analysis of these dy-

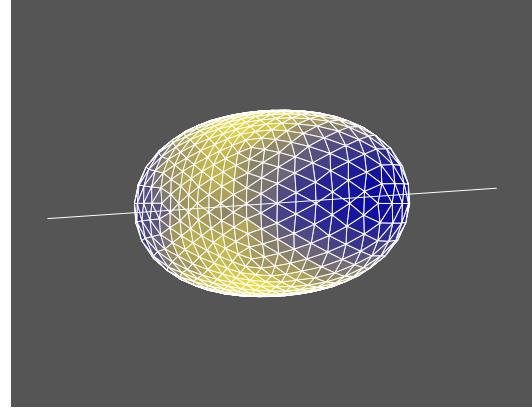


Figure 1: A typical vesicle obtained by simulations. The white line indicates the main axis direction. The color code on the vesicle corresponds to the value of the local curvature, which is large at the tips and low in the central region.

namics constitutes an essential step that is explored in this Letter.

We consider a model system, which is a phospholipid vesicle (Figure 1). We thus ignore in this first exploration the effect of the cytoskeleton. This reduction is essential to identify the basic underlying mechanisms. .

The major results of this study are: (i) We find that the width of the region of parameters where the VB mode is manifested significantly widens upon increasing shear rate. This behavior was not captured by any of the previous theories or simulations. (ii) We find that the period of oscillation in the TT and TB regime is practically independent of the shear rate $\dot{\gamma}$, in marked contrast with a previous numerical study using multiparticle collision dynamics [16]. (iii) We develop an analytical theory that accounts for these two facts. (iv) We demonstrate that the Keller-Skalak theory (which assumes a fixed shape for the RBCs, and is often used as a basis in experiments and theoretical studies) is an excellent framework for TT

and TB description when shape deformability is negligible (small $\dot{\gamma}$ or large λ , the ratio of internal over the external viscosity). However, major deviations are revealed when $\dot{\gamma}$ is large enough and/or λ is not too large. (v) We report on a transition between tumbling and the kayaking phase, during which the main axis of the vesicle rotates around an axis perpendicular to the shear plane. Strikingly, kayaking seems to occur even if the vesicle is initially forced to be in the shear plane.

The Model: The Stokes equations (experiments have so far explored the limit of small Reynolds numbers) can be formally solved using the Boundary Integral (BI) formalism (see for example [21]) which yields

$$\eta_m \mathbf{v}_{mem}(\mathbf{r}) = \eta_{out} \mathbf{v}_{shear} + \int_{mem} \overline{G}(\mathbf{r} - \mathbf{r}') \mathbf{f}_{mem}(\mathbf{r}') d\mathbf{r}' + (\eta_{in} - \eta_{out}) \int_{mem} \mathbf{v}_{mem}(\mathbf{r}') \cdot \overline{K}(\mathbf{r} - \mathbf{r}') \cdot \hat{\mathbf{n}}(\mathbf{r}') d\mathbf{r}' \quad (1)$$

where $\mathbf{v}_{mem}(\mathbf{r})$ is the local velocity field at the membrane, $\mathbf{v}_{shear} = \dot{\gamma} y \hat{\mathbf{x}}$ is the externally applied Couette flow (with $\dot{\gamma}$ the shear rate), $\eta_m \equiv (\eta_{in} + \eta_{out})/2$ (η_{in} and η_{out} stand for viscosities of the internal and external fluid, respectively), \int_{mem} is an integration over the membrane and $\overline{G}(\mathbf{r} - \mathbf{r}')$ and $\overline{K}(\mathbf{r} - \mathbf{r}')$ are the Green tensors defined as:

$$\overline{G}(\mathbf{x})_{ij} = \frac{1}{8\pi} \left(\frac{\delta_{ij}}{x} + \frac{x_i x_j}{x^3} \right); \overline{K}(\mathbf{x})_{ijk} = \frac{3}{4\pi} \frac{x_i x_j x_k}{x^5}$$

A vesicle that is subjected to a flow undergoes a shape transformation that is limited by bending modes. The reaction bending force of a vesicle on the fluid is given by the Helfrich force [22]

$$\mathbf{f}_{curv}(\mathbf{r}) = -\kappa \left[\frac{1}{2} c(\mathbf{r}) \{ c(\mathbf{r})^2 - 4g(\mathbf{r}) \} + \Delta_{2D} c(\mathbf{r}) \right] \hat{\mathbf{n}}(\mathbf{r}) \quad (2)$$

where κ is the bending modulus, $c(\mathbf{r})$ is the local mean curvature ($c(\mathbf{r}) = c_1(\mathbf{r}) + c_2(\mathbf{r})$, c_1 and c_2 are the two principal curvatures at point \mathbf{r} of the membrane), $g(\mathbf{r})$ is the Gaussian curvature ($g = c_1 c_2$), Δ_{2D} is the (surface) Laplace-Beltrami operator on the membrane, and $\hat{\mathbf{n}}$ is the outward unit normal vector. The other contribution to the membrane force follows from local membrane incompressibility:

$$\mathbf{f}_{tens}(\mathbf{r}) = T [\zeta(\mathbf{r}) c(\mathbf{r}) \hat{\mathbf{n}}(\mathbf{r}) + \nabla_{2D} \zeta(\mathbf{r})]$$

where ∇_{2D} is the surface gradient operator and $\zeta(\mathbf{r})$ is a local dimensionless Lagrange multiplier that enforces membrane inextensibility (the constant T has a dimension of energy per unit surface). Local membrane inextensibility sets severe limitations on the numerics, both on the time step and the precision of the results. Carelessness (for example, imposing a small enough tolerance of a few % on area) may induce spurious results. The scheme used in this study ensures an area variation lower than $5.10^{-4}\%$. The precise numerical analysis is a formidable task and technical details will be reported elsewhere. Instead, we focus here on the major outcomes.

Results: The phase diagram of various dynamics (TT, TB and VB) of a vesicle and RBC in a Couette flow recently motivated a large number of theoretical and experimental studies [3, 15, 16, 19, 20]. This is the first focus of our study. Let us introduce appropriate dimensionless numbers. Shape deformability can be measured by the dimensionless number

$$C_\kappa = \frac{\eta_{out} \gamma R^3}{\kappa}$$

where R is the typical size of the vesicle. Vesicles exhibit various equilibrium shapes (i.e., in the absence of flow) [23], depending on their reduced volume $\tau = 6\sqrt{\pi}V/S^{3/2}$, where S is the area of the membrane and V the internal volume. τ is the second dimensionless parameter. For $\tau > 0.652$, the shape is prolate (one long revolution axis) [23]. In the range $0.591 < \tau < 0.652$, the shape is oblate (one small revolution axis; the shape is biconcave, known also for RBCs). We found that, for $C_\kappa \geq 1$ (which is quite easily reachable experimentally), the oblate branch is suppressed in a Couette flow so that only prolate shapes prevail (see Fig.1). The last dimensionless parameter is $\lambda = \eta_{in}/\eta_{out}$. While our study can be performed at different τ , we will consider a reduced volume close enough to unity. This will allow us to compare the theoretical approaches considering the quasi-spherical limit [12, 14, 15, 16, 17]. We have chosen the value $\tau = 0.95$ and have explored the effects of the two other parameters C_κ and λ . The resulting phase diagram is represented in Fig.2.

A first important feature found here is that the boundaries of the phase diagram are strongly underestimated in previous analytical theories [15, 17]. For example, for $C_\kappa \simeq 0.1$, the bifurcation from TT to TB occurs here for $\lambda \simeq 8$, while analytical theories predicted $\lambda \simeq 4$ (Fig.2). This is astonishing because deviation from a sphere is only about 5% and a perturbative scheme is expected to make sense. Thus, we have attempted to understand this peculiar behavior by revising previous analytical theories. The key ingredient is that the next order terms in an expansion in powers of excess area (relative to a sphere) are decisive, however small the deviation from a sphere. We have identified the fact that this is the result of a singular behavior of the expansion scheme. Details of the analytical theory will be given elsewhere [24]. The outcome of this analytical theory is presented in Figure 2, revealing excellent agreement with the full numerical simulation.

Previous analytical [3, 15] as well as numerical calculations [16] (based on dissipative particle dynamics) and experiments [19] reported that the band of existence of the VB mode saturates with C_κ above a value of the order of $C_\kappa \sim 0.5$. This is in good agreement with the present numerical study as long as $0.5 < C_\kappa < 2$. Beyond a value of the order of $C_\kappa = 2$, the VB band exhibits a sudden ample widening as shown in Fig. 2. This ef-

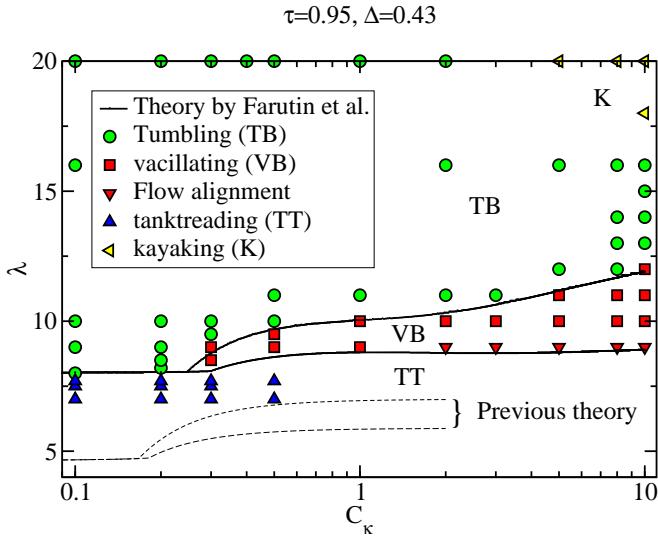


Figure 2: Phase diagram for $\tau = 0.95$. The symbols correspond to numerical results and the solid line to the analytical. The Flow alignment states correspond to a VB mode with a very small amplitude (see Fig.5). These states are thus intermediate between VB and TT. The K phase is visible at the upper right corner of the diagram.

fect highlights the nontrivial character of dynamics due to shape deformation. A careful theoretical analysis of this phenomenon has led us to the discovery that not only is the fourth order harmonic strongly coupled to the second one, but it also acquires strong activity on increasing C_κ . This mode, which is damped at low deformability, becomes active (i.e. it is excited) at larger deformability (larger C_κ). As a consequence, the VB regime is promoted further and further, leading to the VB band widening. We have found that this peculiar behavior is captured by the new theory that implements fourth order harmonics [24].

Let us now analyze the behavior of the tumbling angle $\theta(t)$. It is convenient to represent a phase portrait in the plane $(\dot{\theta}, \theta)$. This will also allow us to shed light on the limit of applicability of the KS theory, which is often used as a basis in experiments [11, 13] and in numerical simulations [16]. We find that, for $C_\kappa \rightarrow 0$ (we choose $C_\kappa = 0.1$ as an example), the simple relation $\dot{\theta}/\gamma = A + B \cos(2\theta)$ predicted by the KS theory is in excellent agreement with the BI simulations.

At larger deformabilities, the situation is more complex and requires a careful analysis. We first focus on the value $\lambda = 20$. The result is reported in Fig.3 (shifted by $+0.5$ upward for clarity). All data for $1 < C_\kappa < 10$ are nearly superimposed, reflecting a good agreement with the KS theory even though, for $C_\kappa \geq 5$, the vesicle is actually kayaking [15]. $\dot{\theta}(t)$ represents in this case the tumbling of the projection of the main axis in the shear plane. In contrast, at smaller values of λ , ($\lambda = 16$ in Fig.3), major deviations from the KS theory are man-

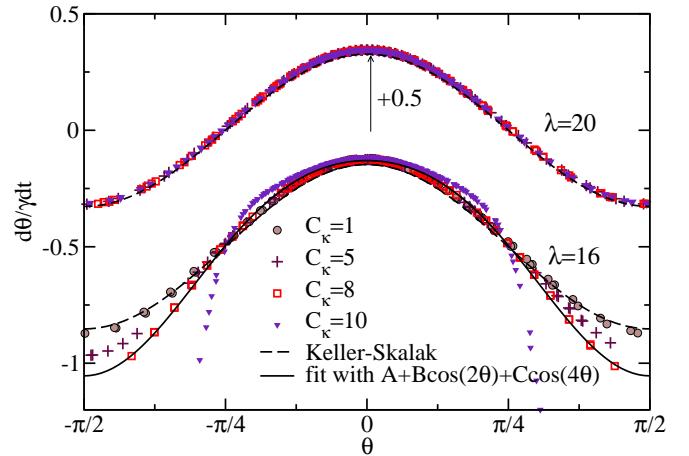


Figure 3: $\dot{\theta}$ as a function of θ for $\lambda = 16$, $\lambda = 20$ (shifted upwards by $+0.5$), for various C_κ . The dashed line corresponds to the KS theory. The full black line is a fit of the data points for $\lambda = 16$ and $C_\kappa = 8$ with the function $A + B \cos(2\theta) + C \cos(4\theta)$ ($A = 0.543$, $B = 0.462$ and $C = 0.049$), showing that higher harmonics play an important role at large deformabilities.

infested. In particular, we observe the excitation of the fourth order harmonic, represented by $\cos(4\theta)$ in the figure when C_k is increased up to 8. Note that, for $C_\kappa = 10$, other higher order harmonics are excited as well, which is a precursor to the TB-VB or the TB-K bifurcation.

We have analyzed several other physical quantities, such as evolution and possible exchanges of the two main axes lying in the shear plane, but we shall focus only on the behavior of the period (scaled by the shear rate) in this brief exploration. The results are shown in Fig.4. A remarkable fact is the quasi-robust character of the rescaled period as a function of the deformation regardless of the dynamical mode (TB, VB or K) (only minor variations by few % are manifested over a range of a decade in shear rate). This finding is not intuitive in as much as deformation (at large enough C_κ) plays an essential role (strong deviation from the KS theory). This result runs contrary to a previous numerical analysis [16] based on dissipative particle dynamics. The ratio of their period variation and ours attains a factor 100. We do not have an explanation about the origin of this major discrepancy. We have checked, in light of the new analytical theory, that the same quasi-independence on C_κ is also manifested.

Finally, it is worth emphasizing that the transient dynamical regime can prove to be very slow, especially at large values of C_κ . It is necessary to ascertain the establishment of a given regime on the scale of the longest time. For large enough λ , the appropriate (slow) time scale is $\tau_\kappa = \eta_{in} R^3 / \kappa$; motion is limited by the more viscous internal fluid. For $C_\kappa = 10$, this may typically represent a hundred cycles in the TB regime. Thus, it is necessary to make use of appropriate and stable numeri-

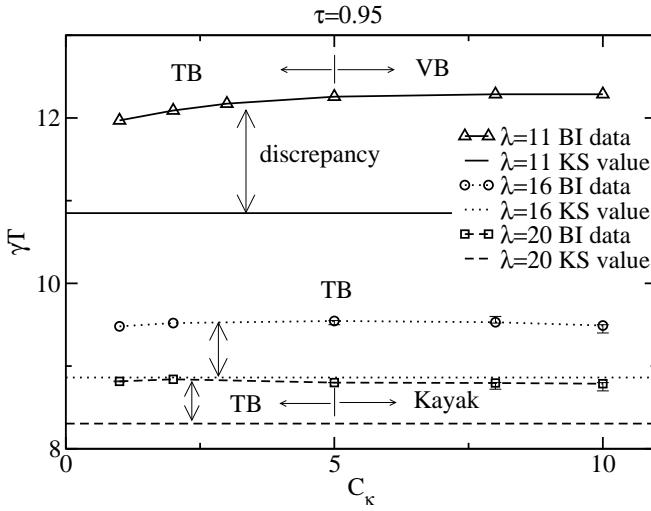


Figure 4: Decoupled tumbling period for $\tau = 0.95$ as a function

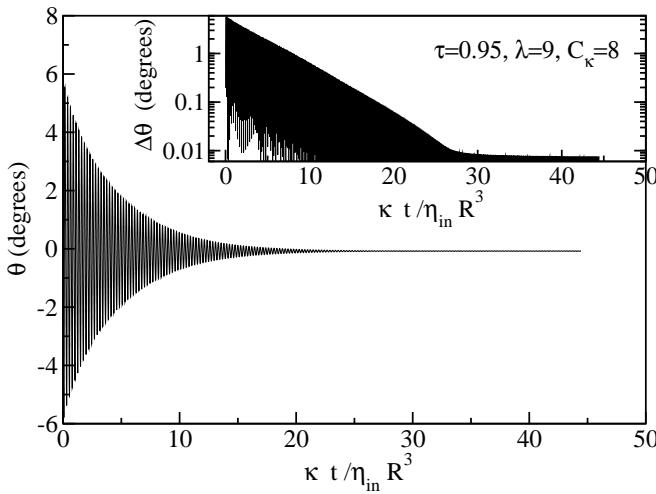


Figure 5: Long time relaxation of the vesicle close to the TT-VB line. The inset shows a log plot of the vacillation amplitude.

cal schemes. Details will be published elsewhere. Here, it suffices to provide an illustration exhibiting the slow relaxation (Fig.5). The VB amplitude close to the TT-VB line ($\lambda = 9$, $C_\kappa = 8$) is shown. We find an exponential relaxation of the VB amplitude (the inset of Fig.5 provides a log plot of the amplitude). The vesicle reaches its steady state only after a characteristic time of about $30\eta_{in}R^3/\kappa$, corresponding to 125 oscillations. The same feature is observed for the TB-K transition.

Conclusion: We have reported on a quantitative numerical analysis in three dimensions that led us to identify new features of vesicle dynamics, which were not revealed in prior analytical, numerical, or experimental studies.

A theory has allowed us to unearth a subtle role played by higher order terms. The theoretical results agree remarkably well with the numerical ones. This work is a first essential step toward a systematic study of RBC dynamics and blood rheology. An obvious limitation of our work is the absence of shear elasticity associated with the cytoskeleton. An analysis that includes this factor constitutes the next natural step.

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